

Severity of Chronic Kidney Disease did not Influence Bleeding during Treatment of Acute Coronary Syndromes

Andrew Lee BA, Jeremy J. Lum MD, Todd B. Seto MD, MPH, Christian Spies MD, and James R. Madison DO

Abstract

We assessed the influence of CKD on bleeding in 200 patients with ACS via retrospective chart analysis. Using K/DOQI guidelines to stratify patients based on GFR, no differences in documented bleeding or antithrombotic utilization were observed among the groups. Due to increased mortality risk of patients with CKD from cardiovascular disease, assessing benefit-to-risk ratios of various medical interventions is crucial.

Introduction

Chronic kidney disease (CKD) is increasing in prevalence in the US among the adult population. Cardiovascular disease including acute coronary syndromes (ACS) accounts for nearly half of all deaths among CKD patients.¹ Reasons for this increased risk of cardiovascular death and morbidity include a higher prevalence of cardiac risk factors in patients with renal dysfunction including smoking, dyslipidemia, hypertension, and hyperhomocystinemia.²⁻⁶ Additionally, it has been shown that medical treatment of ACS using standard medications such as beta-blockers, aspirin, thrombolytics, as well as utilization of percutaneous revascularization techniques are less commonly implemented in patients with CKD as compared to those with normal renal function.⁷⁻¹² Reported explanations for this discrepancy include concerns about bleeding complications as well as the limited available data examining the treatment and outcomes of patients with CKD. The landmark clinical trials studying the use of medical treatments and procedures after myocardial infarction have typically excluded patients with CKD or end-stage renal disease (ESRD). Further, there is no data examining the effect renal dysfunction has on the risk of bleeding in patients being treated for ACS.

The National Kidney Foundation (NKF), in an effort to improve the quality and outcomes of treatment for patients with kidney disease, launched the Kidney Disease Outcomes Quality Initiative (K/DOQI).¹³ This initiative which stratifies patients based on their glomerular filtration rate (GFR), provides criteria for

evaluating and classifying kidney disease, an approach to risk stratification, and evidence-based practice guidelines for continuous care and therapy of CKD. Current work is aimed at formulating practice guidelines for the management of cardiovascular disease, especially ACS in CKD patients.

This study sought to define bleeding risks in CKD patients medically treated for ACS. Using the K/DOQI CKD guidelines to stratify patients based on their degree of kidney disease, we examined the impact of renal dysfunction on documented bleeding events and use of antithrombotic therapy.

Methods

Our study was approved by appropriate institutional review boards. Our collective was identified by a computerized search of discharge diagnoses for ACS and CKD at two major hospitals in Honolulu, HI, from January 2001 to June 2003. Medical records of these visits were accessed, and 200 patients with CKD were randomly selected from those admitted for ACS.

All patients fulfilled American College of Cardiology/American Heart Association (ACC/AHA) criteria for unstable angina or acute myocardial infarction (14). All patients were also required to fulfill criteria for CKD, defined for screening purposes as having a serum creatinine concentration of >1.5 mg/dl. Creatinine clearance was then calculated for all patients according to the Cockcroft-Gault formula: $\text{CrCl} = \frac{[140 - \text{age}] * \text{weight (kg)}}{[\text{serum creatinine (mg/dl)} * 72]}$ (15). Subsequently, patients were grouped into one of four classes based on NKF K/DOQI guidelines for CKD (13): Stage 2 (GFR 60-89), Stage 3 (GFR 30-59), Stage 4 (GFR 15-29), or Stage 5 (GFR <15). Excluded from this study were patients who underwent CABG or received thrombolytic therapy during their hospitalization, as well as those presenting with acute renal failure.

Baseline characteristics and clinical data were extracted from all charts meeting the above criteria. Using TIMI criteria, they were evaluated for bleeding complications, both major and minor events (16).

This work is supported by a grant from the Queen Emma Research Foundation.

- University of Hawaii John A. Burns School of Medicine, Honolulu, HI (A.L., T.B.S.)
- University of Hawaii, Department of Internal Medicine, Honolulu, HI (J.J.L., T.B.S., C.S., J.R.M.)
- University of California Davis, Division of Nephrology, Sacramento, CA (J.R.M.)
- Queen's Medical Center, Honolulu, HI (T.B.S.)
- Rush University Medical Center, Section of Cardiology, Chicago, IL (C.S.)

Correspondence to:
Jeremy J. Lum MD
University of Hawaii Internal Medicine Residency Program
1356 Lusitana Street, 7th floor
Honolulu, HI 96813-2427
Ph: (808) 586-2910
Fax: (808) 586-7486
Email: lumjj@hawaii.rr.com

Table 1.— Baseline Characteristics of Chronic Kidney Disease Patients with Acute Coronary Syndrome, Based on K/DOQI Stage

Characteristic	Stage 2 (GFR 60-89)	Stage 3 (GFR 30-59)	Stage 4 (GFR 15-29)	Stage 5 (GFR <15)
Patients, n	11	38	59	92
Male (%)	6 (55)	32 (84)	32 (54)	42 (46)
Hemoglobin (mg/dl)	13.8 ± 1.9	12.6 ± 2.4	11.1 ± 1.9	11.2 ± 1.8
Platelets (103/ul)	294.5 ± 15.4	226.3 ± 79.6	249.8 ± 103	232.7 ± 71.9
Hypertension (%)	11 (100)	30 (79)	55 (93)	77 (84)
IDDM (%)	2 (18)	10 (26)	21 (36)	29 (32)
NIDDM (%)	2 (18)	8 (21)	14 (24)	14 (15)
Prior History of MI (%)	2 (18)	11 (29)	32 (54)	38 (41)

Continuous data is presented as mean ± SD.

All p-values were non-significant, except for number of females (p=0.003) and baseline hemoglobin (p<0.001).

None of the patients in this cohort had any documented history of bleeding disorders.

IDDM = Insulin-dependent Diabetes Mellitus, NIDDM = Noninsulin-dependent Diabetes Mellitus, MI = Myocardial Infarction.

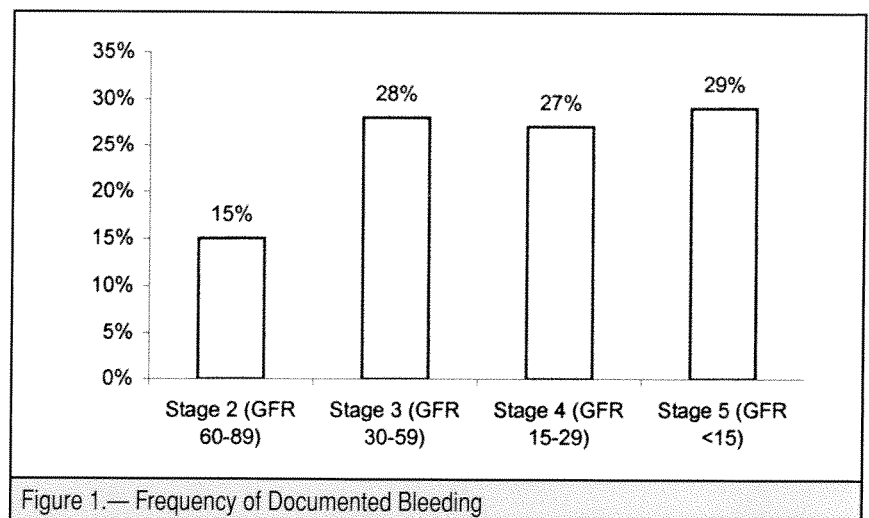


Figure 1.— Frequency of Documented Bleeding

Finally, the in-hospital utilization of ASA, clopidogrel, GPIIb/IIIa-inhibitors, enoxaparin, and IV-heparin was recorded.

Differences between K/DOQI groups were analyzed using ANOVA or chi-square test, as appropriate. Statistical analysis was performed by using the SPSS statistical package, version 10.0 (SPSS Institute, Inc., Chicago, IL). Continuous data are expressed as mean ± SD and categorical data as frequencies and percentages.

Results

We reviewed 200 patients with CKD admitted for ACS. No increased bleeding tendencies, such as known bleeding diatheses, a family history of bleeding disorders, or chronic outpatient Coumadin use, were identified in this cohort. Baseline characteristics between each K/DOQI group were similar (Table 1), except for the Stage 3 group having fewer women compared to the Stage 5 group (16% vs. 54%, p=0.003). Differences in baseline hemoglobin from

Stage 2 to Stage 5 (13.8 mg/dl ± 1.9 vs. 11.2 mg/dl ± 1.8; p<0.001) were also noted. Finally, there was an increasing trend in the number of patients per K/DOQI group, from Stage 2 to Stage 5.

The overall bleeding rate was 27% for the cohort. There were no significant differences among the groups in frequency of documented bleeding (Stage 2, 3, 4, 5: 15%, 28%, 27%, 29% respectively; p=0.872 (NS)) or in mean number of PRBCs transfused (Stage 2, 3, 4, 5: 0.5, 1.0, 1.0, 1.5 respectively; p=0.5249 (NS) (Figure 1).

No significant differences were observed in the utilization of aspirin, clopidogrel, GPIIb/IIIa-inhibitors, enoxaparin, or IV-heparin among the K/DOQI groups (Table 2). Finally, regression analysis did not identify K/DOQI Stage as an indicator for increased bleeding.

Discussion

Despite the event rate being higher than historic controls^{8,17} we were unable to identify whether the

Table 2.— Utilization of Antithrombotic Therapy, Based on K/DOQI Stage

Treatment	Stage 2 (GFR 60-89)	Stage 3 (GFR 30-59)	Stage 4 (GFR 15-29)	Stage 5 (GFR <15)
Aspirin	6 (55)	28 (74)	41 (69)	62 (67)
Clopidogrel	6 (55)	9 (24)	19 (32)	19 (21)
GPIIb/IIIa Inhibitor	4 (36)	4 (11)	8 (14)	4 (4)
Enoxaparin	4 (36)	13 (34)	21 (36)	24 (26)
Heparin	4 (36)	4 (11)	13 (22)	18 (20)

All p-values were non-significant.

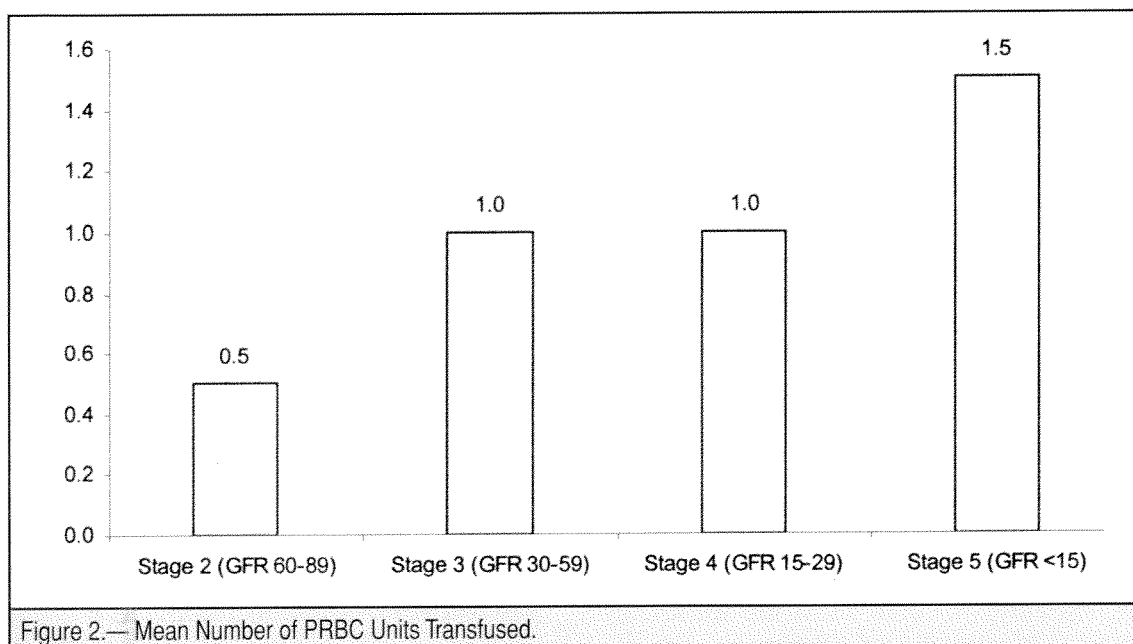


Figure 2.— Mean Number of PRBC Units Transfused.

K/DOQI Stage of CKD had any influence on bleeding risks among those receiving medical treatment for ACS. While not statistically significant, the bleeding rate of patients in Stage 2 was lower than in other stages. Possible explanations include the low number of patients within this group, or perhaps this might represent a threshold of renal dysfunction, where a transition from Stage 2 to Stage 3 may be associated with increased bleeding risk. We will need larger sample size to better evaluate the relationship. While we did observe an increasing trend in the total number of PRBCs transfused as the degree of kidney disease worsened, this may represent the slightly lower baseline hemoglobin level found in those subjects in Stage 4 and 5 being transfused to a similar goal, or perhaps this is an early sign of increased bleeding among those with more advanced kidney disease. Perhaps stronger conclusions could be drawn if specific indications for blood transfusions were known. Finally, no significant differences in the utilization of antithrombotic therapy were observed between K/DOQI groups. This is in contrast to previous studies that have reported decreased use of antithrombotic therapy with increasing renal dysfunction.⁷⁻¹² This

study demonstrated that similar medical therapy among patients with declining renal function did not result in an increased bleeding rate. The major implication of this finding is in the treatment of patients in Stage 4 and Stage 5. With an over-representation of cardiovascular disease occurring among those with CKD, more work is needed to improve outcomes in this population. Because our study is retrospective in design, we can make no conclusions; however it may add to the limited data that the degree of renal failure may not be a limiting factor when determining appropriate medical treatment of CKD patients with ACS.

The overall bleeding rate of this cohort was 27%, higher than reported bleeding rates among non-renal disease patients with ACS.^{18,19} Patients with renal dysfunction demonstrate an increased risk of bleeding, due to defects in platelet function and metabolism, defects in vascular endothelial/smooth muscle cell metabolism, and the influence of anemia on hemostasis.²⁰⁻²² There is also data suggesting that CKD patients have an increased tendency towards occult gastro-intestinal bleeding while undergoing dialysis treatment.^{23,24} However, since our report is

retrospective in design, direct causes of bleeding could not be determined, although it is likely that multiple metabolic or pathologic influences affect bleeding in this collective. The principal observation from this report is that while there appears to be an increased overall bleeding event rate in those with CKD, there does not appear to any difference as the degree of kidney disease worsens.

While there were no statistically significant differences in the use of various medical therapies between K/DOQI groups, the overall utilization of antithrombotic therapy was much lower than reported in patients with ACS and normal renal function.⁷⁻¹² While this study did not address mortality rates of the cohort, other studies have found a consistent and large mortality benefit with increased use of antithrombotics, regardless of the severity of renal dysfunction.^{7,8,11,12}

Several considerations should be made when interpreting this study. This cohort was derived from a retrospective chart analysis and is prone to limitations inherent to such studies. This includes the possibility of unmeasured factors influencing the data and the inability to generate cause and effect conclusions. While all bleeding events were documented, many records failed to document the location of the bleed. Thus, conclusions regarding the possible contraindications of patients not receiving antithrombotic therapy cannot be made. Additionally, potential participant bias may exist, due to large number of Stage 4 and Stage 5 patients treated at surveyed hospitals.

In conclusion, this study found that the severity of renal dysfunction did not influence bleeding risk among patients medically treated for ACS. Currently, all trials regarding treatment and outcomes after ACS have excluded patients with renal insufficiency. Large prospective clinical trials that include patients with CKD are needed to properly assess actual bleeding risks and recommend appropriate interventions in this high-risk population. Presumably, with the development of more aggressive treatment strategies both in the acute setting and in primary prevention, improvements in the quality of care of patients with CKD may be realized.

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